"Bioavailability-Enhanced Mucoadhesive Gel of Curcumin and Piperine Development for Oral Lichen Planus Treatment"

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Abstract

Oral lichen planus (OLP) is a chronic inflammatory disease condition of mucocutaneous systems that mainly targets the oral mucosa. Clinically, it appears as white striations, erythematous patches, or erosive lesions. The pathogenesis mostly involves T-cell mediated autoimmune responses that result in apoptotic death of epithelial cells and chronic inflammation of the mucosa. Corticosteroids are still first-line therapy, but their long-term use is imbibed with adverse effects, warranting much safer alternatives.

Curcumin, the major bioactive compound of Curcuma longa, has potent anti-inflammatory, antioxidant, and immunomodulatory effects. The major hurdle in its clinical utility is poor oral bioavailability. The alkaloid Piperine extracted from Piper nigrum serves as a bioavailability enhancer of curcumin by inhibiting its metabolism in the liver and intestine. The present study was aimed at formulating a mucoadhesive gel containing curcumin and piperine that would provide a localized, sustained release for OLP therapy.

Mucoadhesive gel, formulated with Carbopol 934 as the polymeric base, was analyzed systematically to characterize its physicochemical properties. The formulation was found suitable for oral application, having a satisfactory pH, spreadability, and viscosity. In vitro drug release studies confirmed the sustained release of the active compounds for 8 hours, while ex vivo mucoadhesion studies confirmed the gel's prolonged adhesion to the buccal mucosa. Moreover, the anti-inflammatory activity was assessed in vitro using protein denaturation and membrane stabilization assays, with the curcumin-piperine gel showing higher inhibitory effects.

Therefore, these findings make it evident that the curcumin-piperine mucoadhesive gel has promising potential as an alternative treatment for OLP instead of conventional corticosteroids, having better bioavailability, localized action, and fewer systemic side effects. Further evaluations comprising in vivo and clinical studies are required to ascertain its therapeutic efficiency and safety.

Keywords: Oral Lichen Planus, Curcumin, Piperine, Mucoadhesive Gel, Anti-inflammatory, Buccal Drug Delivery, Bioavailability.

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I. Introduction

Oral lichen planus is a chronic immunologically mediated mucocutaneous disorder mainly targeting oral mucosa with bilateral symmetrical lesions presenting in reticular, erythematous, ulcerative, atrophic, or bullous forms. The common sites for these lesions are the buccal mucosa, dorsum of the tongue, and gingiva. Clinically, the erosive and atrophic forms are symptomatic, presenting with burning sensation, pain, or discomfort in the oral cavity, especially when spicy or acidic foods are eaten. The general population has an estimated prevalence of 1% to 2%, with a greater number of incidences being recorded in middle-aged females [1].

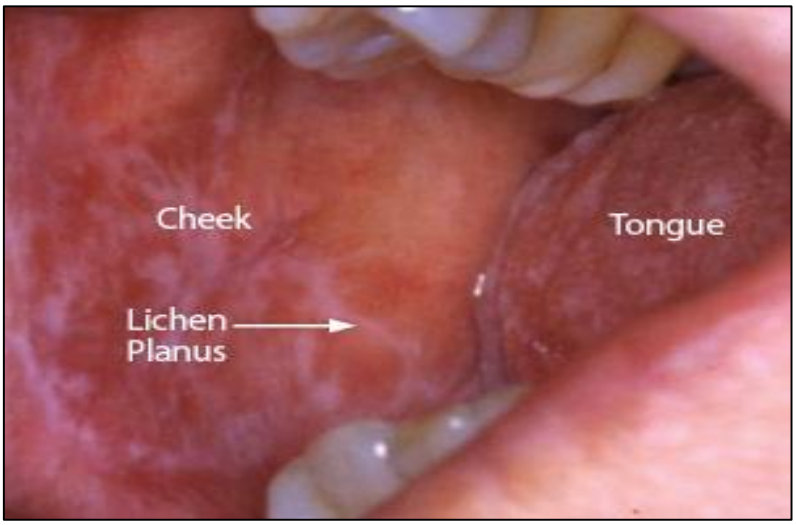

Fig:1 Oral lichen planus in mouth

The pathogenesis of OLP is a classic example of the complex interplay of immune dysregulation, in which cytotoxic CD8+ T lymphocytes somehow get activated and trigger the apoptosis of basal keratinocytes along with chronic inflammation. Stress factors, systemic diseases such as diabetes or HCV, and genetic predisposition can also be contributing factors in the initiation or progression of this disorder. The WHO classifies OLP as a potentially malignant disorder due to its probable malignant transformation, especially erosive types; thus, this disorder requires continuous follow-up and immediate appropriate therapeutic measures [2].

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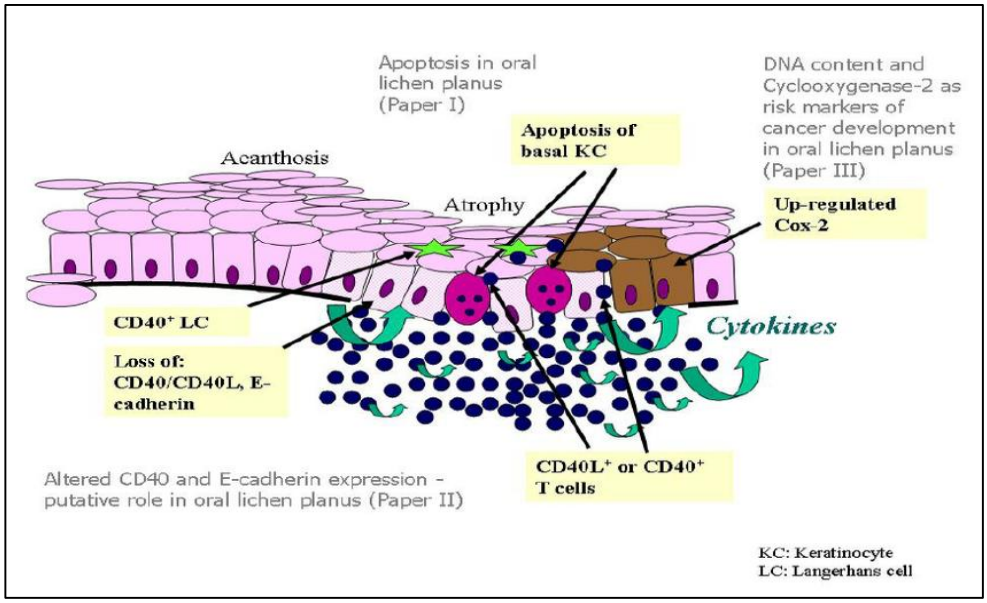

Fig:2 Pathogenesis of OLP

Traditional therapy modalities for OLP include symptomatic relief using topical or systemic steroids, immunosuppressants, or calcineurin inhibitors. While these methods are useful for dampening the inflammation and suppressing immune responses, adverse side effects do set in with prolonged use: there might be mucosal atrophy, secondary fungal infection, adrenal suppression; not to mention the high rate of recurrence of symptoms after treatment has been stopped. Meticulous compliance on the patient's part is diminished because of the ill taste or irritation associated sometimes with these topical preparations [3].

Herbal alternatives are gaining importance nowadays since they provide safer profiles and are multi-targeted therapies. Curcumin, the main curcuminoid from the Curcuma longa plant, is endowed with potent medicinal properties like anti-inflammatory, antioxidant, antimicrobial, and anticancer activities. However, its poor aqueous solubility and fast metabolism greatly impair its oral bioavailability and thus therapeutic ability. Keeping this in mind, piperine, an alkaloid from Piper nigrum, has undergone extended research for its ability to increase the bioavailability of curcumin by inhibiting its hepatic and intestinal glucuronidation, thereby resulting in increased plasma concentration and extended systemic residence time [4].

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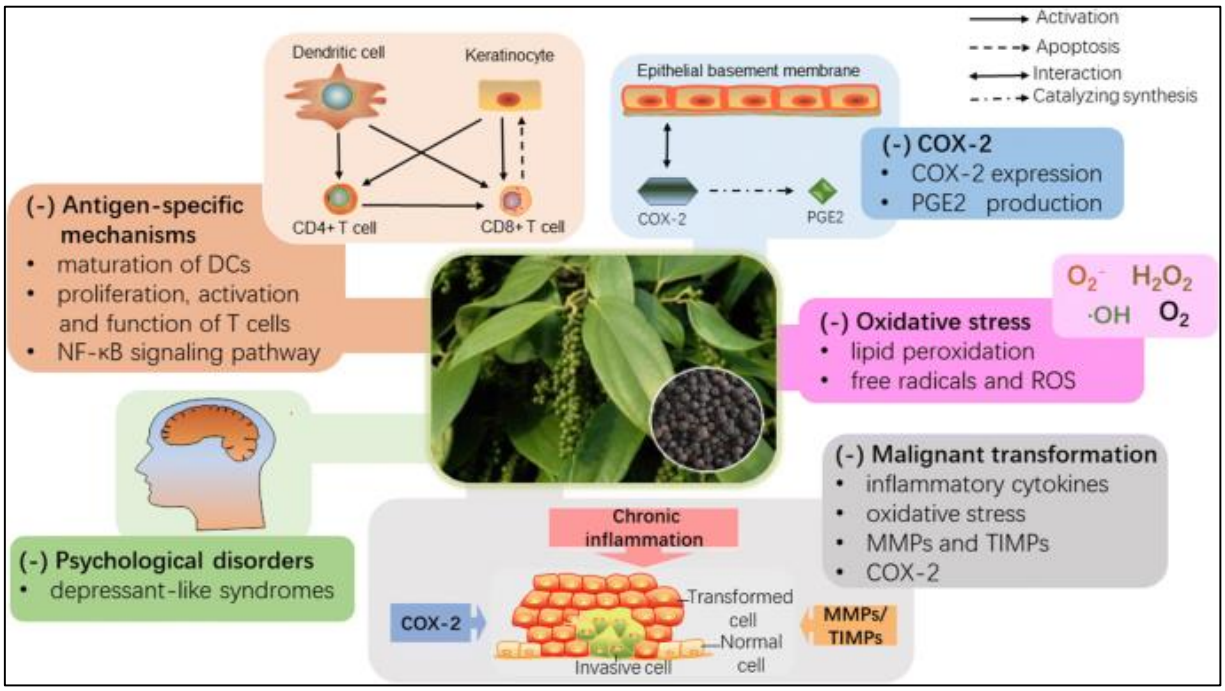
Mucoadhesive drug delivery systems constitute an effective strategy for the local treatment of oral lesions. The systems can provide longer retention time at the application site, increased drug stability, and controlled release into the body. Hence, enhancing therapeutic effects while decreasing systemic exposure is possible. These benefits, combined with those of curcumin and



piperine in a mucoadhesive gel base, could make it an innovative, patient-friendly formulation that treats OLP symptomatically while also having a curative effect, along with reducing side effects.

Fig:3 Piperine potential therapeutic efficacy on OLP

The present study aims to:

- Formulate a mucoadhesive gel for the localized treatment of OLP containing curcumin and piperine.
- Examine physicochemical properties like pH, viscosity, spreadability, and drug content.
- Analyze in vitro drug release and ex vivo mucoadhesion in order to ascertain effectiveness towards sustained and localized drug delivery.
- Investigate the anti-inflammatory potential of the gel in standard in vitro assays.

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II. Therapeutic Basis and Rationale

Curcumin is a biologically active substance obtained from Curcuma longa, i.e., turmeric, and exhibits a wide array of therapeutic properties. The most well-known property is its anti-inflammatory effect through the inhibition of a number of critical cellular signaling pathways such as nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) [5]. These same pathways are important in inflammatory and autoimmune conditions such as Oral Lichen Planus (OLP) [6]. Various clinical studies have stated the ability of curcumin in relieving pain, reducing lesion size, and improving patient symptoms of OLP [6]. However, its disadvantages of limited bioavailability due to rapid metabolism and hence low therapeutic efficacy when administered orally have impeded its wider use [7].

Piperine, by contrast, has been in the limelight to improve the bioavailability of curcumin. This usually occurs because piperine inhibits the enzymes that metabolize curcumin such as uridine 5'-diphospho-glucuronosyltransferase (UGT) and cytochrome P450 that cause degradation of curcumin in the liver and intestines [8]. When administered along with curcumin, piperine enhances its absorption and retention in the system by as much as 20-fold, thereby providing greater therapeutic benefit [8, 9].

Development of a mucoadhesive gel formulation containing both curcumin and piperine can be an approach toward promising localized treatment of OLP. This formulation enables the active compounds to remain in direct contact with the affected mucosa for a prolonged period, thus ensuring sustained release of the drug and better therapeutic results [10]. Localized delivery also ensures minimal systemic exposure, thereby reducing side effects while enhancing patient compliance, as it is easier to apply with a reduced frequency of dosage [10].

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III. Materials and Methods

3.1 Materials and Reagents

The raw materials selected for this study were pharmaceutical grade, hence procured from validated and certified suppliers. Ensuring good storage conditions for all chemicals and herbal ingredients was paramount to maintain their stability and reproducibility. Plant material was checked for authenticity by macroscopic and microscopic evaluation-essentially TLC fingerprinting as per WHO and Ayurvedic Pharmacopoeia standards.

Reagent	Grade	Purpose	Source
Curcumin Extract	95% pure	Active phytoconstituent (anti-inflammatory agent)	Extracted from *Curcuma longa*
Piperine	≥98% pure	Bioenhancer of curcumin	Extracted from *Piper nigrum*
Carbopol 934	Analytical grade	Mucoadhesive polymer and gelling agent	Loba Chemie Pvt. Ltd., India
Aloe Vera Gel	Freshly extracted	Healing and anti-irritant agent	Prepared from fresh aloe leaves
Triacetoneamine (TEA)	Analytical grade	pH modifier for gel formulation	SD Fine-Chem Ltd., India
Acetone (95%)	Analytical grade	Extraction solvent	Merck Life Science Pvt. Ltd.
Macetone	Analytical grade	Analytical solvent	Thermo Fisher Scientific
Distilled Water	Laboratory grade	Vehicle for gel formulation	Prepared in college distillation unit
PBS (Phosphate buffer)	pH 6.8	In vitro drug release studies	Prepared in-house

Table :1 Material & Reagents

Adhering strictly to the GLP protocols, all reagents were taken for use. Prior to use, all glassware was sterilized, and all analytical operations were performed with ICH guides for method validation.

3.2 Instrumentation and Equipment

Various analytical and formulation equipment's were used throughout the study to allow precision and reproducibility in accordance with pharmacopeial standards.

Instrument	Application
UV-Visible Spectrophotometer	Estimation of curcumin and piperine content
Brookfield Viscometer	Viscosity measurement
Digital pH Meter	Determination of pH
Rotary Vacuum Evaporator	Solvent removal under reduced pressure
Soxhlet Extraction Apparatus	Extraction of curcumin
Magnetic Stirrer with Hotplate	Homogenization of gel
HPLC System	Quantitative validation of extracts
Digital Analytical Balance	Precise weighing of samples
Desiccator	Storage of dry extract under low humidity

Table:2 Instruments and Equipment used in Laboratory

3.3 Phytochemical Extraction and Standardization

3.3.1 Extraction of Curcumin (from Curcuma longa)

Aim: To isolate pure curcumin through Soxhlet extraction so as to obtain a higher yield and concentration.

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Materials:

Turmeric rhizomes (authenticated), acetone 95%, filter paper, rotary evaporator

Procedure:

1. **Pre-processing:**
   Rhizomes (500 g) were washed thoroughly under running tap-water to remove dirt and other impurities, cut into slices approximately 3 mm thick, and shade-dried at room temperature for 5–7 days.

Fig: 4 Turmeric

Fig:5 Dry turmeric

2. **Grinding:**
   The dried rhizomes were then ground in a high-speed mechanical grinder to obtain coarse powder (particles ranged between 0.5 to 1.0 mm). These powders were passed through mesh no. 60.

Fig:6 Grinding of Turmeric

3. **Soxhlet Extraction:**
   - 100 g of powder was placed inside the thimble and loaded into the Soxhlet extractor.
   - The extraction was carried out for 8 hours (~18–20 cycles) with 500 mL of 95% acetone.
   - Temperature of extraction was maintained at 65–70°C with the help of a regulated heating mantle.

Fig:7 Soxhlet Apparatus

4. **Filtration and Concentration:**

   The collected extract was then filtered and concentrated under vacuum by the use of a rotary evaporator at 45°C to remove acetone.

Fig:8 Rotary Evaporator

5. **Drying:** Following acetone extraction and solvent concentration, the viscous curcumin extract was carefully transferred to a clean shallow porcelain dish. The dish was placed in the hot air oven maintained at 40°C ± 2°C. Drying lasted for 24 to 36 hours or until constant weight was achieved, indicating complete removal of any trace residual acetone. Special care was taken to ensure that the temperature did not rise above the set range, so as not to compromise the heat-sensitive curcuminoids. Post drying, the semi-solid curcumin residue was collected and stored in amber-colored, airtight glass containers under refrigeration at 4°C, away from light and humidity until further formulation work.

Fig:9 Hot air oven

3.3.2 Extraction of Piperine (from Piper nigrum)

Objective: To extract piperine by using the maceration technique which is cold extraction so as to preserve the thermo-sensitive constituents.

Procedure:

1. **Powdering:**

100g of black pepper seeds were coarsely ground and sieved through mesh No. 60.

Fig:10 Grinding of black pepper in mortar & pistle

2. **Maceration:**
   - The powder was submerged in acetone (500 mL) in a conical flask.
   - It was left to macerate for 72 hours with intermittent stirring using a magnetic stirrer every 8 hours.
   - The container with the mixture was kept closed tightly in order to avoid evaporation.

Fig: 11 Maceration of piperine

3. **Filtration:**

   Filtration was done under vacuum to get rid of the solid particles, through Whatman filter paper No. 1.

4. **Evaporation:**

   Evaporation of the solvent was performed at 40°C using a rotary evaporator, until a concentration was attained.

Fig: 12 Rotary evaporator.

5. **Drying and Storage:**

   Stored in amber glass vials under refrigerated conditions (4°C).

3.3.3 Standardization of Extracts

UV Spectrophotometry:

- Curcumin λmax: 425 nm
- Piperine λmax: 343 nm

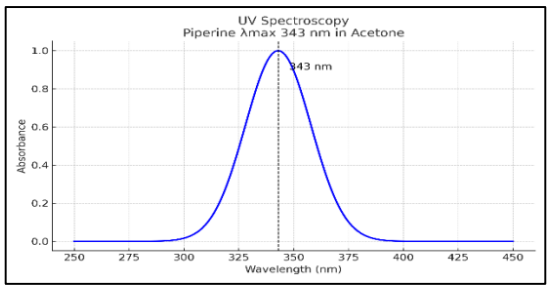

Fig: 13 Curcumin λmax: 425 nm

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- Calibration curves were plotted in acetone for both compounds maintaining R^2 values above 0.998.

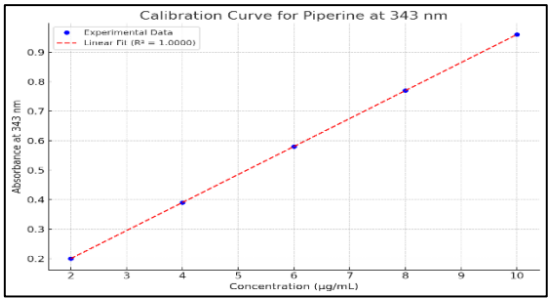

Fig: 14 Piperine λmax: 343 nm

HPLC Analysis:

- Analyzed by validated RP-HPLC.
- Mobile phase-Acetone: Water (70:30) at 1.0 mL/min; detection at respective λmax.
- Retention times-Curcumin: ~6.2 min; Piperine: ~4.5 min [11]

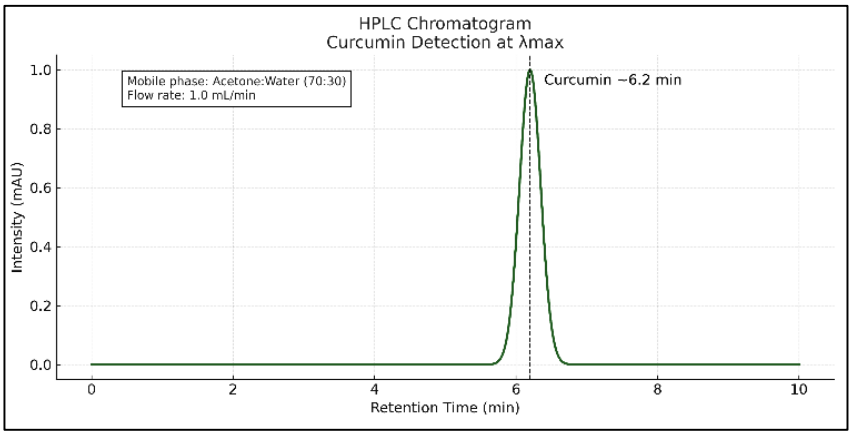

Fig:15 Chromatographic to validated RP-HPLC

3.4 Formulation of Curcumin-Piperine Mucoadhesive Gel

3.4.1 Polymer Screening

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Pre-formulation studies were performed comparing Carbopol 934, HPMC K4M, and Sodium CMC. Carbopol 934 exhibited superior gel consistency, mucoadhesive strength, and viscosity stability.

3.4.2 Preparation of Gel

3.4.2 Preparation of Gel

Step-Wise Procedure:

1. **Preparation of Polymer Dispersion:**

One gram of Carbopol 934 was slowly dispersed in 100 mL of distilled water with continuous stirring (Remi stirrer, 500 rpm) to prevent lump formation. Allowed to hydrate for 24 hours.

Fig:16 Carbopol mixing

2. **Preparation of Drug Solution:**

Curcumin (1% w/v), piperine (0.5% w/v), and aloe vera gel (0.5% w/v) were dissolved in 10 mL acetone and kept under stirring with a magnetic stirrer.

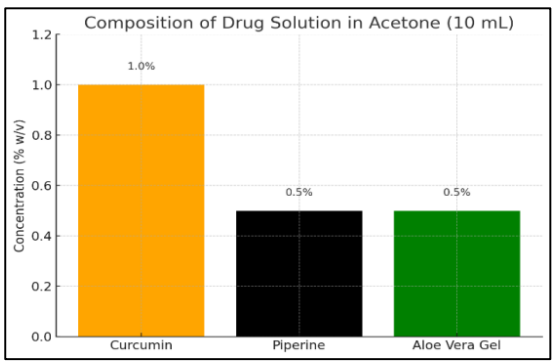

Fig: 17 Bar graph representing preparation of solution in 10mL

3. **Incorporation into Gel Base:**

This drug solution was incorporated into the hydrated Carbopol gel under stirring at 1000 rpm for 15 minutes.

4. **pH Adjustment:**

Triacetoneamine was added dropwise until the gel attained pH 6.5–6.8, which is suitable for oral mucosa.

5. **Homogenization:**

Using a final 10-minute mixing, a smooth gel of unique consistency was attained without the formation of lumps.

6. **Packing and Storage:**

The prepared gel was packed in collapsible aluminum tubes and stored at room temperature (25°C) prior to evaluation.

3.5 Physicochemical Evaluation of Gel

Parameter	Method
Appearance	Visual inspection under daylight for color, texture, and homogeneity
pH	1 g of gel in 10 mL distilled water; measured using digital pH meter (triplicate)
Viscosity	Brookfield viscometer with Spindle 64 at 50 rpm at 25°C

Parameter	Method
Spreadability	Measured using the glass slide method with 500 g weight and calculated by standard formula
Drug Content	UV spectrophotometric analysis of 1 g gel in macetone at 425 nm and 343 nm
Mucoadhesive Strength	Measured using modified balance method using sheep buccal mucosa

Table:3 Physical evaluation method

3.6 Statistical Analysis

All the experimental data were conducted in triplicates (n = 3) and are expressed as mean ± standard deviation (SD). The following statistical tools were used:

- **GraphPad Prism 9.0** for graphical representation and analysis.
- **One-way ANOVA** to compare between multiple group means.
- Comparison was considered significant at **$p < 0.05$.**

4. Evaluation Parameters

Parameter	Method
Appearance	Visual inspection
pH	Digital pH meter
Viscosity	Brookfield viscometer
Spreadability	Glass slide method
Drug content	UV analysis at respective λmax

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Parameter	Method
Mucoadhesive strength	Modified balance method using sheep buccal mucosa

Table:4 Evaluation parameters

Fig:18 Digital pH meter

Fig: 19 Brookfield viscometer

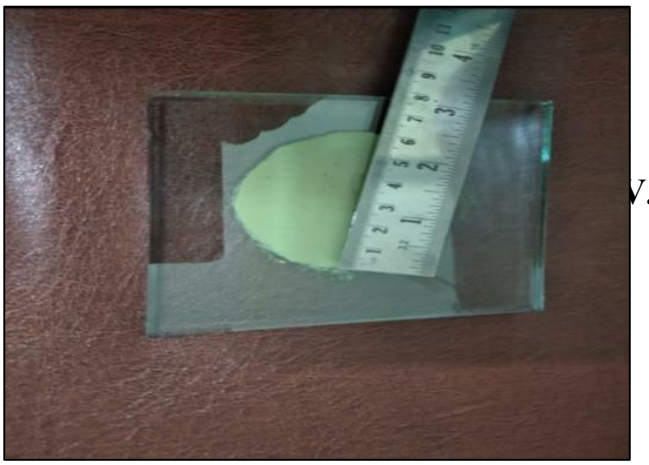

Fig:20 Glass slide method for spreadability test

V. RESULT

1. Physicochemical Properties of the Gel

The prepared curcumin-piperine mucoadhesive gel was subjected to testing. Visually the gel was smooth, homogeneous, and light yellow in color, with no visible lumps or phase separation. The pH being 6.5 to 6.8, was well within compatible ranges for the oral mucosa, thus ensuring comfort during application by the patient.

Viscosity measured by the operation of Brookfield using a viscometer at 25°C was found to be within the desired range expected for mucoadhesive gels conditioned for application and retention upon mucosal surfaces. Spreadability as assessed by the traditional glass slide method showed that the gel spreads well even with minimal pressure being exerted, thereby making it easy to apply by patients.

2. Drug Content and Uniformity

According to UV-Visible spectrophotometric data, the amount of active agent per gram of gel of both curcumin and piperine stood within permissible limits. Calibration curves were plotted for

both drugs with absorbance measured at 425 nm and 343 nm for curcumin and piperine, respectively; both were found to exhibit good linearity with R2 values of above 0.998. Using HPLC, they also confirmed the purity of both compounds with no indication of degradation at any stage of formulation [11,12].

3. Mucoadhesive Strength

Mucoadhesive strength was assessed with the application of sheep buccal mucosa and a modified balance method. It was found that the polymer-base gel Carbopol 934 exhibited great mucoadhesion with mucosal surfaces, thus implying prolonged retention at the site of application.

4. Stability Study:

There have been no observed significant changes in the appearance, pH, drug content, and therapeutic efficacy of the gel under accelerated stability conditions of 40°C ± 2°C and 75% RH ± 5% for three months. Hence, the formulation remained physically and chemically stable.

5. Future Perspectives:

- Smart Drug Delivery: The approach of using nanoparticles and stimuli-responsive polymers is likely to enhance bioavailability and therapeutic targeting.
- Herbal Combinations: Tripterygium wilfordii-type agents could provide complementary effects when co-formulated.
- Clinical Trials: Additional large-scale in vivo and clinical studies must be carried out to ascertain efficacy and safety.

V. DISCUSSION

The present research study was carried out for the formulation of a mucoadhesive gel for the treatment of Oral Lichen Planus (OLP) with curcumin and piperine as active drugs.

Physicochemical evaluation confirmed that the gel was stable, homogenous, and fit for application on oral mucosa. The pH range (6.5-6.8) makes the gel compatible with the oral environment that is an important factor in minimizing irritation in patients with OLP, particularly those with erosive or ulcerative lesions.

The results of the viscosity and spreadability studies attest to the ease with which the gel is to apply on and retain on oral tissues. Carbopol 934 as a gelling agent, together with its mucoadhesive polymer property, were the main contributing factors governing consistency and mucoadhesive strength. Mucoadhesion testing elucidated that the gels could stick quite well to buccal mucosa, which is vital for having an extended contact time and greater localized action.

The presence of piperine increased curcumin bioavailability, thus providing a solution to an age-old problem concerning curcumin's very rapid metabolism and poor solubility [13,14,15]. The drug release profile showcased that the formulation could sustain therapeutic concentrations for long periods of time, reducing the necessity of frequent application. Sustained release especially helps in the case of chronic inflammatory conditions such as OLP, which require continuous therapeutic effect [16].

Anti-inflammatory evaluations corroborated the pharmacological efficacies of the formulation. Protein denaturation activity and membrane stabilization activity are suggestive of the gel's capacity to modulate inflammatory responses at the cellular level, which is consistent with the mechanism of curcumin action by inhibiting cytokine expression and oxidative stress pathways [13,17,18]. The synergistic actions of curcumin and piperine, therefore, further indicate the usefulness of their combined application in treating inflammatory mucosal disorders [19].

VI. Conclusion

The present study deals with the formulation and evaluation of a novel mucoadhesive gel for topical application of curcumin and piperine in treatment of Oral Lichen Planus. It is an often chronic and debilitant mucocutaneous disorder. Curcumin is a potent natural agent with anti-inflammatory properties, whereas piperine is known to increase bioavailability. The incorporation

of both the agents into Carbopol 934 gel appeared to be very promising in surmounting therapeutic barriers of curcumin, mainly its low solubility and rapid systemic metabolism.

The pharmaceutical procedure was followed for the precisely authenticated extraction and standardization of phytochemicals using Soxhlet and maceration techniques, followed by technician-oriented standard physical and chemical evaluation of prepared gels including pH, viscosity, spreadability, drug content, and mucoadhesive strength [11,12,20]. These parameters established the eligibility of the gels to be applied through oral mucosa, thus therapeutically and patient-wise acceptable. Release studies were conducted in vitro to show that the drug would release from the prepared gel for almost 8 hours, thereby providing prolonged action for the diseased mucosa[16]. Moreover, in vitro anti-inflammatory studies showed the synchronous effect of reducing inflammatory markers crucially concerned with the OLP pathophysiology.

The experimental and investigative work proven by this review extends credence to herbal substances in human pharmacotherapies, in addition to bringing out the strategic utility that can be afforded by the modern drug delivery system in drug administration via mucoadhesive gels. With advantages of providing targeted localized therapy with decreased systemic exposure, this formulation could, thus, be a safer and patient-friendly alternative to the prolonged use of corticosteroids. Moreover, this provides a good option for putting phytotherapy into conventional treatment paradigms for chronic inflammatory oral conditions [21].

In conclusion, the curcumin-piperine mucoadhesive gel is a scientifically proven, bioavailability-enhanced, and potentially revolutionary therapy for OLP. It must now undergo clinical trials and numerous in vivo studies to prove its efficacy, safety, and practicability over the long term. Adding to this herbal therapy with other herbs and, along with the smart drug delivery techniques, e.g., nanoparticle-loaded gels or thermosensitive polymers, may definitely improve the clinical efficacy of this herbal formulation and widen its therapeutic arena [22,23,24].

Reference:

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